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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,308	09/07/2005	James R. Eshleman	58556-US (71699)	6007

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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10/12/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,308	ESHLEMAN ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/30/09, 12/8/09, and 6/24/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 5, 15, 41-43, 45, and 59-66 and 69-72* is/are pending in the application.

4a) Of the above claim(s) *59-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,15,41-43,45 and 69-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed March 30, 2009, Applicant's Amendment and Remarks filed December 8, 2009, and Applicant's Amendment filed June 24, 2010.

Claims 67 and 68 have been canceled. New claims 71 and 72 are acknowledged. Claims 1 and 41-43 have been amended.

Claims 1, 5, 15, 41-43, 45, and 59-66 and 69-72 are pending in the instant application.

Claims 59-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely made the restriction (election) requirement without traverse in the reply filed on March 24, 2008.

Accordingly, claims 1, 5, 15, 41-43, 45, and 69-72 have been examined on the merits.

Response to Amendment

Applicant's Amendment and Remarks filed December 8, 2009 is acknowledged. It is noted that the instant application is fully compliant with the sequence rules of 37 CFR 1.821-1.825. Applicant's Amendment filed June 24, 2010 is acknowledged. It is noted the instant application is fully compliant with the requirements of 37 CFR 1.121(c).

Oath/Declaration

In the previous Office Action mailed October 29, 2008, the oath or declaration was indicated to be defective. Applicant's resubmission of a new oath filed December 8, 2009 is acknowledged. It is noted that the new oath is compliant with the requirements 37 CFR 1.67.

Drawings

In the previous Office Action mailed October 29, 2008, the drawings were objected to because some of the Figures were color photographs, where only black and white Figures have been submitted. Applicant's Replacement Figures filed March 30, 2009 are acknowledged. It is noted that Applicants have also made amendments to the specification in the transmittal papers filed March 30, 2009 to remove any reference to color drawings. In view of these submissions, **this objection is withdrawn**.

Nucleotide Sequence Disclosures

In the previous Office Action mailed October 29, 2008, it was noted that the application contained sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2), but which were not so identified. In view of Applicant's Amendment and Remarks filed December 8, 2009, the instant application is fully compliant with the sequence rules of 37 CFR 1.821-1.825.

Specification

In the previous Office Action mailed October 29, 2008, the disclosure was objected to because the specification contained embedded hyperlinks and/or other forms of browser-executable code that are impermissible and must be deleted. In view of Applicant's Amendment to the Specification filed March 30, 2009, **this objection is withdrawn**.

Claim Objections

In the previous Office Action mailed October 29, 2008, claim 41 was objected to because the word, "wherein" was recited twice, back-to-back. **This objection is withdrawn** in view of Applicant's Amendment to claim 41 filed March 30, 2009.

Claim Rejections - 35 USC § 112.

In the previous Office Action mailed October 29, 2008, claims 1, 5, 15, 41-43, 45, and 67-70 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, or an *in vitro* method for selectively treating cells comprising an infectious disease organism, the methods comprising targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one

stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule, does not reasonably provide enablement for an *in vivo* method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state, or an *in vivo* method for selectively treating cells comprising an infectious disease organism, the methods comprising targeting the nucleic acid molecule with an oligonucleotide; and binding of the oligonucleotide to the target nucleic acid molecule; wherein the oligonucleotide comprises a backbone nucleic aid sequence, and two arm nucleic acid sequence, and wherein the backbone nucleic acid sequence is complementary to one stand of the target nucleic acid molecule and the arms are complementary to the other strand of the target nucleic acid molecule, thereby inhibiting transcription of the target nucleic acid molecule. **This rejection is withdrawn against claims 67 and 68** in view of Applicant's Amendment filed March 30, 2009 to cancel these claims. **This rejection is maintained** against claims 1, 5, 15, 41-43, 45, 69 and 70 for the reasons of record set forth in the previous Office Action mailed October 29, 2008. It is noted that new claims 71 and 72 are also included in this rejection.

Response to Arguments

In response to this rejection, Applicants argue that the Specification lists references that teach molecular based approaches to target cells. Applicants point the Examiner to page 2 of the disclosure, for example. Applicants also argue that the specification does not need to contain an example if the invention is disclosed in such a

manner that one skilled in the art would be able to practice the invention without an undue amount of experimentation.

Applicants contend that the Specification provides ample data to support a method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state or a method for selectively treating cells comprising an infectious disease organism, as claimed. Applicants point the Examiner to Example 2, Example 3, Example 4, and Example 8, for example. Applicants also contend that the Specification describes a number of methods known in the art that have been used for gene delivery *in vivo*. Applicants point the Examiner to pages 22 and 23 of the Specification. In view of these arguments, Applicants contend that the methods as instantly claimed are enabled by the instant disclosure.

These arguments and contentions have been fully considered, but are not found persuasive by the Examiner. Regarding an *in vivo* method for inhibiting replication or transcription of a nucleic acid molecule indicative of a disease state or an *in vivo* method for selectively treating cells comprising an infectious disease organism, the methods comprising the administration of an anti-gene lock of Applicant's invention, Shi et al. (Journal of Antimicrobial Chemotherapy, 2008 Feb;61(2):262-72. Epub 2007 Dec 22) teach that such *in vivo* methods are unpredictable.

Shi et al. teach anti-gene padlocks eliminate *E. Coli* based on their genotype. For example, Shi et al. teach that anti-gene padlocks (AGPs) bound in a sequence-specific manner and inhibited DNA synthesis *in vitro*. Shi et al. explicitly teach:

> "In this study, we report a novel potential cell killing technique, AGPs, and demonstrated that they bound in a

> sequence-dependent manner to their target genes and inhibited DNA synthesis *in vitro*"
>
> "Although the purpose of these experiments was primarily to demonstrate proof-of-principle of this novel cell killing approach, it is tempting to speculate about their future potential as novel therapeutics"
> "There are other general issues that will complicate delivery of oligonucleotides in whole animals. First, delivery of AGPs to cells may be difficult since AGPs are extremely large and anionic. Second, a large amount of oligonucleotide will likely be needed due to their high molecular weight. Third, standard DNA oligonucleotides are degraded by serum. In addition, the efficiency of oligonucleotide uptake by bacterial cells is estimated to be <10%... The combination of these issues results in significant impediments to clinical use of the agents and it is certainly likely that this strategy would be restricted to infections that cannot be treated using conventional antimicrobial agents"
>
> "While the AGPs were designed to intertwine with both DNA strands, we demonstrated DNA synthesis inhibition *in vitro* only"
>
> "Eliminating eukaryotic cell populations using AGPs will likely be more difficult"

Given these explicit teachings, it is clear that the *in vivo* use of anti-gene locks, as described in Applicant's invention is unpredictable. Furthermore, based on these teachings, the specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the claimed methods in *in vivo* environments.

A review of the instant application fails to find adequate guidance or any disclosure exemplifying the *in vivo* applications as broadly claimed. Although, Applicants clearly recognize the potential of inhibiting transcription of the target nucleic acid molecule *in vivo* using anti-gene locks, Applicants do not teach the ordinary artisan how to effectively deliver anti-gene locks to target cells *in vivo* to inhibit transcription of

the target nucleic acid molecule. No technical guidance or exemplary disclosure is provided regarding the use of the claimed methods for inhibiting transcription of the target nucleic acid molecule in living organisms using the anti-gene locks of Applicant's invention. As the reference of Shi et al. above indicates, anti-gene locks have been used to inhibit DNA synthesis *in vitro* only. Furthermore, as Shi et al. indicate, due to the size, anionic nature, and high molecular weight of anti-gene locks, their delivery into cells is highly complicated, which results in significant impediments for clinical use. Such experimentation represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success. Due to the broadness of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation with a large number of subjects and controls to determine how to successfully deliver AGPs to cells *in vivo*.

Thus, it is maintained that the prior art at the time of Applicant's filing would not enable the use of anti-gene lock therapeutics *in vitro* to support claims directed to the *in vivo* use of anti-gene locks, let alone claims directed to delivering anti-gene lock therapeutics *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments of inhibition to the *in vivo* methods of inhibiting transcription of the target nucleic acid molecule using AGPs, as exemplified in the reference above.

In order to practice the invention using the specification and the state of the prior

art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those anti-gene locks that inhibit transcription of the target nucleic acid molecule that are successfully delivered to target sites in appropriate cells (*in vivo*) such that transcription of the target nucleic acid molecule is inhibited. Since the specification fails to provide any real guidance for methods of using anti-gene lock therapeutics *in vivo*, and since resolution of delivering anti-gene locks in a living organism is unpredictable, one of skill in the art would have been unable to practice the invention, commensurate in scope with the claims, without engaging in undue trial and error experimentation.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed October 29, 2008, claims 1, 5, and 15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gibson et al. (Clinical Cancer Research, 2000 Vol. 6:213-222) in view of Escude et al. (Proc. Natl. Acad. Sci., 1999 Vol. 96:10603-10607, Applicant's Reference #1 on the Information Disclosure Statement filed March 4, 2005). **This rejection is withdrawn** in view of Applicant's Amendment filed March 30, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to claim 1 to recite that backbone nucleic acid sequences are complementary to one strand of the target nucleic acid molecule and arms are complementary to the other strand of the target nucleic acid molecule, where the oligonucleotide backbone has one or more mismatches with the target

nucleic acid sequence. It is noted that the references of Gibson et al. and Escude et al. do not teach or suggest this claim limitation.

After careful reconsideration of the claims, a new ground(s) of rejection is made of record as detailed below:

Claim Objections

Claims 69-72 are objected to because of the following informalities: Claims 69-72 are exact duplicates of each other. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-43 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41-43 and 45 are indefinite because while the preamble of claim 41 recites, “a method for selectively treating cells comprising an infectious disease organism”, the methods steps conclude with administering an oligonucleotide sequence, thereby inhibiting transcription of the target nucleic acid molecule. There is not a clear nexus between the purpose of the claim as stated in the preamble and the last method

step. Thus, it is unclear how the method steps accomplish the purpose of the claim as stated in the preamble. Appropriate correction is required.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Terra Cotta Gibbs/
October 7, 2010